

## The Association of Endometriosis and Phthalate Exposure: A Meta-Analysis of Observational Studies

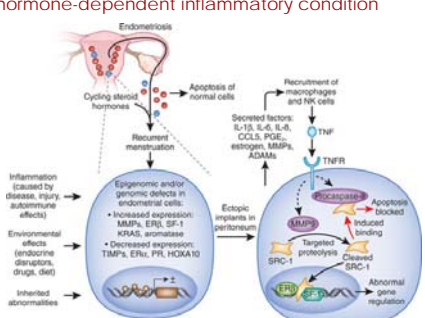
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NEEP 2015  
Occupational / Environmental Health Session  
Oct 1<sup>st</sup>, 2015 (3:45pm-5:00pm Livingston 4)

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## Endometriosis

- hormone-dependent inflammatory condition



[http://www.nature.com/nm/journal/v18/n7/images\\_article/nm.2855-F1.jpg](http://www.nature.com/nm/journal/v18/n7/images_article/nm.2855-F1.jpg)

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Q&A

## Phthalate

-it's all around us



Photos: Shawn Campbell, Mack Sigg, Stephen Cummings

<http://saferchemicals.org/wp-content/uploads/sites/3/2013/05/phthalates-infographic.png>

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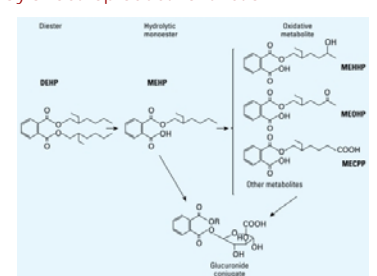
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## Exposure to Phthalate

- may affect reproductive function



[http://open.nlm.nih.gov/imgs/512/341/2790499/2790499\\_elp-117-14811.png](http://open.nlm.nih.gov/imgs/512/341/2790499/2790499_elp-117-14811.png)

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## Research Aim

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True Association?

Elevated phthalate metabolites ↔ Endometriosis patients

Observational Studies

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## Research Method

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- Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group Reporting format

Search Criteria and Eligibility Criteria → Data Extraction → Data Synthesis → Statistical Analysis → Assessment of Study Quality

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## Search Criteria and Eligibility Criteria

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- PubMed/MEDLINE and EMBASE (upto September 16<sup>th</sup>, 2015)
- MeSH term  
("endometriosis"[MeSH Terms] OR "endometriosis"[All Fields]) AND ("phthalic acid"[Supplementary Concept] OR "phthalic acid"[All Fields] OR "phthalate"[All Fields])
- Inclusion criteria
  - case-control studies
  - be conducted on human adults
  - have urinary phthalate metabolites as the exposure measurement (must have urinary MEHP concentration)
  - have endometriosis as the outcome
  - report mean and standard deviation or standard error of the effect estimate

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## Data Extraction

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- 3 reviewers independently extracted data using standardized form
  - For data analysis
    - year of publication
    - study design
    - study population
    - study size
    - exposure chemical
    - sample type
    - exposure level
    - OR and 95% CI
    - description of interpretation of odds
    - outcome measurement methods
    - controlled variables
  - For quality of publication
    - definition and description of cases and controls
    - non-response rate
    - description and definition of exposure measurement

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## Data Synthesis

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- OR of the highest exposure group compared to the lowest exposure group
- Continuous exposure
  - Use median and geometric mean of the urinary MEHP concentration of the total population and converted exposure to dichotomous variable

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## Studies included for meta-analysis

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```

    graph TD
      A[Identified records through database searching after removing duplicates (n=31)] --> B[Studies for full abstract and data screening (n=9)]
      A -.-> C[22 studies excluded for not meeting inclusion criteria:  
1-not relevant to the question  
2-not human study  
13-not case-control study  
2-wrong intervention  
3-wrong outcome  
1-duplication]
      B --> D[Studies included in final analysis (n=5 with 6 cohorts)]
      B -.-> E[4 studies further excluded:  
3-no extractable data  
1-not desired sample type (plasma MEHP)]
    
```

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## Studies Included in Meta-Analysis

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Study (Year)/ Country	Case/ Control (n)	Exposure measurement LOQ (ng/mL)
Upson (2013)/ USA	92/195	0.2
Louis et al (2013)/ USA (Operative cohort)	190/283	0.1
(Population cohort)	14/113	
Weuve et al (2010)/ USA	87/1020	Not reported
Itoh et al (2009)/ Japan	57/80	3X the SD of the method blank test
Huang et al (2010)/ Taiwan	28/29	0.55

Measurement method

- Exposure
  - SPE
  - HPLC-MS/MS
- Outcome
  - Surgical visualization
  - Laparoscopy result
  - Pathological results

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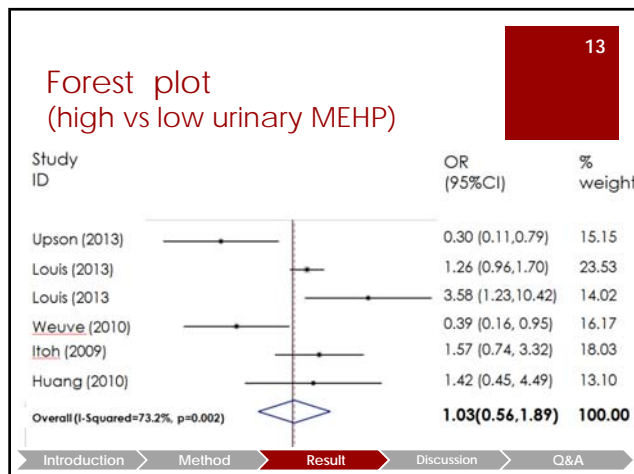
## Assessment of Study Quality

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- Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

	Selection	Comparability	Outcome
Upson et al., 2013	☆☆☆☆	☆☆	☆☆☆
Buck Louis et al., 2013 (population cohort)	☆☆	☆☆	☆☆☆
Buck Louis et al., 2013 (Operative cohort)	☆☆	☆☆	☆☆☆
Weuve et al., 2010	☆☆☆☆	☆☆	☆☆☆
Itoh et al., 2009	☆☆	☆☆	☆☆☆
Huang et al., 2010	☆☆	☆☆	☆☆☆

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### Study heterogeneity

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- meta-regression to evaluate different sources of heterogeneity
  - study country
  - study size
  - exposure range

→ the OR of endometriosis for studies taken place among the US population was lower than those among Asian countries by a factor of 0.5721 (p=0.543)

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### Source of heterogeneity

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- diagnostic methods for endometriosis may partially account for the variation among the results of the included studies
- One study recruited subjects from infertility clinic → selection bias

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### Study limitation?

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- MEHP has short half life (excrete within 1-4 hours)
  - Limit the ability to study long term effect of phthalate exposure
- Other subspecies of phthalate ester acid
  - Highly correlated
- Non-linear association
  - Simple dichotomous method cannot capture the trend

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## What did we find?

- No association between urinary MEHP level and endometriosis was found by meta-analysis
- However, we could not rule out the risk on reproductive health from phthalate exposure, considering the study the limitations.

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## Questions?

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## Additional slides

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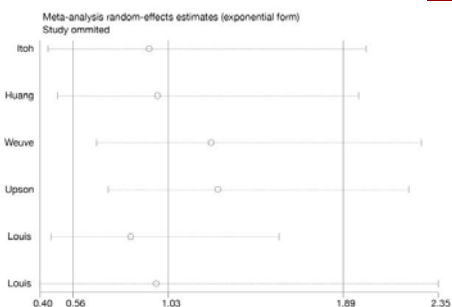
## Statistical Analysis

- Random-effects model
- Heterogeneity:
  - Standard  $I^2$  test
  - meta-regression
  - subgroup analysis
    - geographical location, the number of cases and controls, and the range of phthalate exposure
- Sensitivity analysis
- Funnel plot to assess publication bias
- Egger's regression test to test for asymmetry

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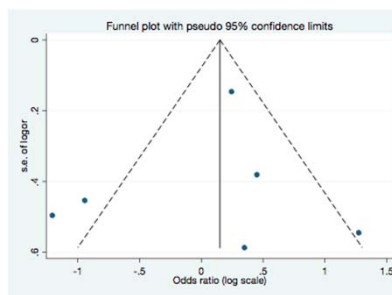
### Sensitivity analysis



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### Funnel Plot for Assessing Publication Bias



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